How to tip the Harm-Benefit-Scales in gene editing – and why legal regulations always trump personal and public beliefs in project evaluation in animal research

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Abstract: Directive 2010/63/EU on the protection of animals used for scientific purposes (henceforth "the Directive") mandates that every project proposal in EU member states involving procedures on living non-human vertebrates and cephalopods must be approved in a project evaluation which includes a harm-benefit-analysis assessing "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations and may ultimately benefit human beings, animals or the environment". This project evaluation is carried out by competent authorities, with the advice of committees whose composition varies across Europe. The committees usually include scientific and veterinary/animal welfare expertise. They also often have experts in legal and ethical issues, advisors on alternatives to animal experiments, and sometimes also lay people. This invites the question: How do committee members understand "ethical considerations", and how does this influence their evaluation and their advice to competent authorities? This is important, for decision-making in project evaluation is restricted and must fall within the boundaries of the applicable legal regulation. We argue that committee members are not always aware of this restriction. Genetic enhancement (e.g. for better modelling of human diseases in larger animals) and disenhancement (e.g. genetically reducing research animals' ability to suffer) are controversial procedures in animal research. Where these two procedures are concerned, the mainly consequentialist and pathocentric legal framework of the Directive will potentially contradict the personal beliefs of some committee members, and indeed some members of the public, about what is morally permissible in animal research. Both genetic enhancement and genetic disenhancement could be classified as a valid benefit by the Directive, but some committee members might consider them morally unacceptable as a result of their personal beliefs. We use this potential conflict to address the question of what happens when committee members are of different opinions; we explain how, under these circumstances, a standardised understanding of "ethical consideration" can be achieved. We argue that, since project evaluation must comply with the normative framework of the Directive, the law always trumps objections based on personal and public beliefs that are in turn based on non-pathocentric and non-consequentialist moral theory. Our argument and its implications can be summarised as follows: First, the authorising committee's benefit evaluation, "taking ethical considerations into account", is restricted to by limits given in the regulation. However, second, it is far from clear that committee members understand what this means. Third, genetic disenhancement and genetic enhancement are arguably two paradigmatic cases where the personal beliefs of committee members will potentially contradict the Directive, and thus where there is real risk of illegal project evaluation. To minimise this risk, committee members should be trained and educated about their role and responsibilities in project evaluation. Only then will it be safe to assume that they are carrying out their authorising role appropriately.

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How to tip the Harm-Benefit-Scales in gene editing – and why legal regulations always trump personal and public beliefs in project evaluation in animal research

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Abstract

Directive 2010/63/EU on the protection of animals used for scientific purposes (henceforth "the Directive") mandates that every project proposal in EU member states involving procedures on living non-human vertebrates and cephalopods must be approved in a project evaluation which includes a harm-benefit-analysis assessing "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations and may ultimately benefit human beings, animals or the environment". This project evaluation is carried out by competent authorities, with the advice of committees whose composition varies across Europe. The committees usually include scientific and veterinary/animal welfare expertise. They also often have experts in legal and ethical issues, advisors on alternatives to animal experiments, and sometimes also lay people. This invites the question: How do committee members understand "ethical considerations", and how does this influence their evaluation and their advice to competent authorities? This is important, for decision-making in project evaluation is restricted and must fall within the boundaries of the applicable legal regulation. We argue that committee members are not always aware of this restriction. Genetic enhancement (e.g. for better modelling of human diseases in larger animals) and disenhancement (e.g. genetically reducing research animals' ability to suffer) are controversial procedures in animal research. Where these two procedures are concerned, the mainly consequentialist and pathocentric legal framework of the Directive will potentially contradict the personal beliefs of some committee members, and indeed some members of the public, about what is morally permissible in animal research. Both genetic enhancement and genetic disenhancement could be classified as a valid benefit by the Directive, but some committee members might consider them morally unacceptable as a result of their personal beliefs. We use this potential conflict to address the question of what happens when committee members are of different opinions; we explain how, under these circumstances, a standardised understanding of "ethical consideration" can be achieved. We argue that, since project evaluation must comply with the normative framework of the Directive, the law always trumps objections based on personal and public beliefs that are in turn based on non-pathocentric and non-consequentialist moral theory. Our argument and its implications can be summarised as follows: First, the authorising committee's benefit evaluation, "taking ethical considerations into account", is restricted to by limits given in the regulation. However, second, it is far from clear that committee members understand what this means. Third, genetic disenhancement and genetic enhancement are arguably two paradigmatic cases where the personal beliefs of committee members will potentially contradict the Directive, and thus where there is real risk of illegal project evaluation. To minimise this risk, committee members should be trained and educated about their role and responsibilities in project evaluation. Only then will it be safe to assume that they are carrying out their authorising role appropriately.

1. Introduction

Directive 2010/63/EU (henceforth "the Directive") on the protection of animals used for scientific purposes requires every project proposal in EU member states with procedures involving living non-human vertebrates and cephalopods to be approved in a review process ([1]). The review evaluates whether the project is justified from a scientific or educational point of view (predicted scientific or educational benefit), whether the purpose justifies the use of animals, and whether the project is designed to be performed in the most humane way possible ([1], article 38). The project evaluation also assesses the severity classification of the procedure ([1]); and it checks compliance with the principle of the 3Rs ([2]) (replacement, reduction, refinement), which states that animal use is only authorised if the research goal cannot be achieved using alternative non-animal methods, or with cognitively "less developed" species, fewer animals and/or less harmful methods.

This part of the evaluation, which is largely scientific and involves rather well-defined project criteria, requires scientific expertise. But the project evaluation also includes a so-called harm-benefit analysis (HBA), to assess "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment" ([1], article 38 d). Here, ethical considerations are applied to determine whether the goal of the experiment is sufficiently important to justify the harms caused to the animals. This assessment mirrors the idea that experiments – even if they are perfectly sound according to scientific criteria – may be disproportionate and should thus be rejected.

In practice, responsibility for carrying out the HBA falls to national authorities. Therefore, member states have set up competent authorities to regulate and administer the evaluation and authorisation of animal research projects.[3] This means that authorisation may be granted by a single person working at a governmental agency, while the evaluation is usually carried out by a group of people, or (henceforth) "committee", with diverse backgrounds and areas of expertise. On the committee there may be scientific researchers, veterinary/animal welfare experts, NGO representatives, lay people, and others.[3] The competent authorities (advised by committees) decides whether the requirements of article 38 mentioned above are met. This decision is not solely scientific in nature – it involves an evaluation which "takes ethical considerations into account" in weighing harms against expected benefits.

The scientific evaluation mentioned in the first paragraph above is relatively well defined. It is much less clear what is to be understood, within an HBA, by "taking ethical consideration into account". In no small part, this is because the Directive is silent on the meaning of "ethical considerations". There is a risk, given this interpretative vacuum, that the evaluations of advising committees will be influenced by personal beliefs. In what follows we shall explain why this is problematic, referring to the role of regulatory ethics and the principle of legality. We will go on to identify specific roles for committee members, and to indicate limitations on what they and the competent authorities are permitted to consider in making project evaluations.

2. The Role of committee members in project evaluations, and limits to the factors they should consider

As mentioned above, the authorisation of project proposals in an HBA depends on the weighing of expected benefits against expected harms, "taking ethical considerations into account". We shall argue that the role of ethical considerations here is limited to the

boundaries of the legal framework ([4]). Our argument is based on the "principle of legality", which requires all laws in constitutional states to be clear and ascertainable. On this principle, authorities must decide on legal matters by applying explicit legal rules ([4]). In the case of animal research, this implies that decision-making on the permissibility of research proposals has to be based on, and is limited to, the normative framework of the Directive – i.e. authorities and committees carrying out a harm-benefit analysis, and thus "taking ethical considerations into account", are limited in their decision-making by implicit and explicit normative criteria created by the Directive. Importantly, this means that personal beliefs, or widely held public beliefs, that are not compatible with the given legal framework must not be allowed to influence the decision-making process. The ethical considerations that are valid within a legal framework have been termed "regulatory ethics" ([4]).

Now, to understand the role of ethical considerations in the Directive, competent authorities and advising committees have to understand what moral theory the Directive is based on. The Directive, with its focus on the 3Rs principle and on weighing harms against benefits, appears to be based mainly on pathocentric and consequentialist moral theory (although the upper limit of permissible pain is a deontological exception to this that is worth noting ([4], recitals 23)). Within this normative framework, the use of animals is morally acceptable as long as the pain, distress and suffering is outweighed by expected benefits, and as long as the pain, distress and suffering does not go beyond a specific threshold which is considered to be impermissible irrespective of the potential benefits of the project. Importantly, the Directive, when it mentions harm, pain, distress and suffering, is almost exclusively concerned with sentient (negative) experiences and omits non-sentient forms of harm such as major interference with an animal's appearance or capacities, humiliation and excessive instrumentalisation (these are referred to in the Swiss regulation ([5]), for example).

This has important scope implications: it limits the opinions, moral theories and objections that can legally be considered in decision-making connected with project evaluation. Specifically, personal or widely held public beliefs, and moral reasons that are incompatible with the normative framework of the Directive, which might merit consideration in a different context, such as moral philosophy or politics, must not interfere with decision-making on a legal basis in project evaluation: decisions must be based exclusively on pathocentric and consequentialist moral theory.

3. Genetic modifications of research animals

In the following discussion we will use fictional (but realistic) examples of genetic enhancement and disenhancement in research animals to illustrate the way in which the personal beliefs of committee members, the attitudes of the authorities, and moral theories, might create objections to the normative framework of the Directive. We will ask what implications these objections might have for project evaluation – in other words, we will discuss whether the concepts of harm underlying the objections are relevant within the framework of the Directive.

With the advent of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing[6] has become unprecedentedly precise, cheap and easy. The technique can be used not only in mice, but also in non-human primates, where it now makes genetic modification feasible. The generation of genetically modified large animals is especially interesting for those working on neurological diseases. Rodents often fail adequately to recapitulate the human disease phenotype here, and therefore rodent studies have limited clinical potential ([7]). But now, by genetically manipulating non-human-primates, knowledge can be generated which a) cannot be gained in other species, and b) is crucial in the development of new

treatments for human diseases. In this article, we use the term "genetic enhancement". We do so because concern has been expressed that genetic modification of the brains of "higher" species potentially enhances (or even "humanise") their cognitive abilities.[8] (We should note in passing that we are not necessarily convinced that, in these higher animals, cognitive ability and the capacity to suffer is increased. However, for the sake of the argument we shall assume this is so. Importantly, if our argument is sound for animals whose capacity to suffer and cognitive abilities are increased, it will also be sound for other animals.)

Paul Thompson coined the term "animal disenhancement" to refer to genetic modifications which reduce animals' capacities in ways that allow them to better suit their environment ([9]). With the recent advances in our understanding of the molecular processes underlying pain physiology, in the near future CRISPR could potentially make it feasible to genetically modify research animals to reduce or erase their ability to feel pain and suffer ([10,11,12,13]). The aim will be to modify the affective dimension of pain (so-called "caring about" the painful sensation ([10]) and/or chronic pain symptoms), while leaving the acute pain response intact ([14]). This would mean that while the animals suffer less, or not at all, they will still show "normal" guarding behaviour as well as "normal" species-specific behaviour as to their non-modified kin.

3.1 Objections to genetic enhancement and disenhancement in animal research

With their potential benefits in prospect, genetic enhancement of non-human primates ([7,15,16]) and genetic disenhancement of rodents ([10,17]) have both been presented as approaches opening up exciting new avenues of research. However, concerns have been raised about each of them. There is of course the general objection to all genetic modification of research animals on religious grounds, or on the basis that it is "unnatural". From a deontological point of view it has also been argued that it is never morally permissible to use animals as a mere means. More specifically, Tom Regan's animal rights theory entails that it is never permissible to use an "experiencing subject of a life" as a means to an end. From a virtue ethics or biocentric point of view, opponents would probably not approve of genetic modifications with a negative impact on the flourishing of the affected individual – a case in point here is the possibility that as a result of the highly developed cognitive abilities of non-human primates it might be difficult to house them adequately in a laboratory setting that allows them to flourish. Yet others are of the opinion that genetic interventions represent a violation of animals' dignity, or a major interference with their appearance or abilities. Turning finally to cases where pain perception is genetically limited, opponents might raise the concern that this represents a technological fix for a moral problem, namely that the animals are suffering for scientific purposes in the first place.

This list is by no means comprehensive – it could be much longer. It serves merely to illustrate the plethora of objections to the genetic enhancement and disenhancement of research animals. It is important to see that the objections are both non-sentientistic and non-consequentialist in nature. However, by contrast the catalogue of examples given in Annex VIII of the Directive ([1]) to illustrate the severity classification of procedures demonstrates that the Directive is almost exclusively concerned with sentient forms of harm viewed in a consequentialist normative framework. There are two exceptions to this involving non-sentient harm: "prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards" and "breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype" ([1], Annex VIII). Both are classified as "mild" pain, distress and suffering. Interestingly, all procedures classified as moderate or severe cause sentience-related forms of harm. Thus in the Directive non-sentient

harms play only a minor role in determining pain, suffering and distress; sentience-related harms are given much more weight. From this it follows that the non-sentientistic objections we have listed above are treated as having no, or very little, relevance to project evaluation in the Directive.

3.2 Potential harms caused by the genetic enhancement of non-human primates according to Directive 2010/63/EU

The rationale for genetically modifying non-human primates in our example is that through such modifications better models of human neurodegenerative disease phenotypes with the potential to bring greater clinical benefits can be created. This raises the question: Within the framework of Directive 2010/63/EU, what potential harms and benefits of using non-human primates for modelling human neurodegenerative diseases are recognised?

In addressing this question, we can point out, first, that the relevant modifications may enhance non-human-primates' cognitive abilities and their ability to suffer. Second, non-human primates seem to be given a somewhat higher moral status in the Directive than other animals ([1], recitals 17, 33, 49, articles 8,31,32). The Directive states: "Due to their genetic proximity to human beings and to their highly developed social skills, the use of non-human primates in scientific procedures raises specific ethical and practical problems in terms of meeting their behavioural, environmental and social needs in a laboratory environment. Furthermore, the use of non-human primates is of the greatest concern to the public" ([1], recital 17). The Directive also demands that non-human primates shall not be used unless "the procedure cannot be achieved by the use of species other than non-human primates" ([1], article 8). From this it follows that their use, albeit restricted, is not prohibited. Their "higher" moral status, together with their greater potential to suffer, just means that the threshold for a positive evaluation regarding compliance with the 3Rs and the HBA is higher: The principle of "relative replacement" aims to replace larger and (supposedly) cognitively more highly developed species with rodents – at least, where the study objective can be reached in the cognitively less developed species. However, especially in the case of neurodegenerative disease it has been questioned whether this is possible in species other than non-human primates ([7]). Furthermore, as long as the increase in expected benefit – which, more often than not, is the rationale for using larger animals in the first place – outweighs the potential increase in suffering connected with the genetic modifications, the requirement of a positive HBA might still be met. The increase in suffering will create objections only if the relevant suffering increases beyond the permissible threshold of pain mentioned in the Directive. However, the painful, but still permissible, procedures listed in the Directive ([1], Annex VIII) suggest that the genetic modifications involved in the study of neurodegenerative disease would not necessarily go above that threshold. From this it follows that genetically modifying non-human primates is, at least in theory, compatible with the framework of the Directive. Also, objectors would need to explain how the expected knowledge could a) be gained in a cognitively less developed species (relative replacement) or b) does not outweigh the (sentience-related) harm. Alternatively, they would need to show c) that the procedure exceeds the threshold of morally permissible pain.

3.3 Potential harms caused by the genetic disenhancement of rodents according to Directive 2010/63/EU

Genetic disenhancement involves genetically modifying research animals so that they suffer less. Once again, this raises the question: Within the framework of Directive 2010/63/EU,

what potential harms and benefits of genetically reducing rodents' ability to suffer are recognised?

The disenhancement could greatly reduce sentient forms of pain, distress and suffering. These are often classified as *moderate* or *severe*, and they include pain and suffering associated with "models of induction of tumours, or spontaneous tumours, that are expected to cause moderate pain or distress or moderate interference with normal behaviour; breeding of genetically altered animals which are expected to result in a phenotype with moderate effects; irradiation or chemotherapy with a sublethal dose" ([1], Annex VIII). At the same time, genetic disenhancement could introduce harms that are classified as *mild* – e.g. harms associated with "prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards" and "breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype" ([1], Annex VIII). This suggests that the disenhancement would result in a net benefit, as judged on the consequentialist scales of the Directive, and comply with the 3Rs requirement: "refine" (without necessarily affecting the number of animals used), "reduce" (the numbers) and "replace". It would at the same time help to secure a positive outcome in the HBA, since the amount of harm that would need to be outweighed will be greatly reduced. Thus, from the pathocentric and consequentialist standpoint of the Directive, there seems to be no objection to such genetic enhancement.

To summarise, we have mentioned several objections which, theoretically, could be raised against the genetic enhancement or disenhancement of research animals. Many of these objections concern non-sentient forms of harm. However, as we have demonstrated, these objections have very little, or no, relevance within the pathocentric and consequentialist framework of the Directive. We have concluded that, in theory, both genetic enhancement and disenhancement are in compliance with the normative framework of the Directive. In the last part of this paper, we will discuss the implications of this for project evaluation.

4. Legal regulation trumps personal beliefs and moral reasoning

The objections mentioned above, while potentially of great relevance in the context of political, public and academic discussion, are of little significance in project evaluation. The Directive is almost exclusively concerned with sentient forms of harm. It offers no place for non-sentientistic and non-consequentialist objections to research procedures. However, the fact that these objections have been put forward suggests that they may be reproduced in advising committees. This is important, mainly for two reasons. First, as explained above, authorisation by competent authorities is based on the principle of legality, and it is limited to the normative boundaries of the legal regulation. Second, the competent authorities are advised (and influenced) by committees. This is especially interesting in the light of a study in Germany evaluating the work of committee members. In the study, approximately 20% of respondents based their ethical evaluation on "intuition and personal moral judgement" ([18]). Interestingly, almost 25% of the respondents raised concerns about "insufficient education in ethics and insufficient criteria for the evaluation" ([18]). This shows that committee members are not always aware of the legal limits of project evaluation and the moral theory underlying those limits, and would welcome assistance with ethical evaluations. The fact that members sometimes base their evaluation on personal beliefs raises the concern that the advice they give to the authorities is potentially being influenced by objections based on non-sentientistic and non-consequentialist considerations. As explained above, these objections have no, or very little, relevance in project evaluation within the normative framework of the Directive. The only objections that are to be weighed within the authorisation process are those based on pathocentric and consequentialist moral theory, and if, as it would appear, committee

members are not always aware of this, they need training and education. Otherwise, there is a risk that their advice to the competent authorities will be incorrect, and that authorisations and rejections in project evaluation will be based on illegal grounds.

5. Conclusion

Genetic enhancement and disenhancement raise ethical concerns that go beyond the pathocentric and consequentialist framework of the Directive. These concerns are likely to be shared, to an extent, by the committee members who advise the competent authorities in project evaluations. However, the principle of legality and the normative framework of the Directive require the competent authorities to base their authorisations and rejections exclusively on pathocentric and consequentialist moral theories that are compatible with the normative framework of the Directive. It would appear that committee members are not always aware of this restriction, suggesting that there are training and education needs here, and specifically that the role and limitations of competent authorities in project evaluation require clarification. Only then can it be safely assumed that the decision-making process will not go beyond the legal regulations.

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